

A Pharmaceutical composition for Angiotensin  
II-mediated diseases

InsB17

Field of the invention

5           This invention relates to a pharmaceutical  
composition for angiotensin II-mediated diseases, which  
comprises a compound having angiotensin II antagonistic  
activity or a salt thereof in combination with a  
10       compound having diuretic activity or a compound having  
calcium antagonistic activity, and to a method of its  
use.

Background of the invention

Diuretic drugs, due to their having mild  
hypotensive effects, have long been clinically used as  
15       antihypertensive agents. However, as undesirable side  
effects caused by the use for a long time, influences  
on metabolism, for example, hypokalemia, hyperuricemia,  
hyperlipemia and diabetes melitus, have been taken up.  
While calcium antagonists have been used as therapeutic  
20       agents of circulatory diseases such as hypertension,  
cardiac diseases, cerebral apoplexy, nephritis and  
arteriosclerosis, it has also been known that they tend  
to cause such undesirable side effects as tachycardia,  
hypotension, erythroprosopalgia and encephalagia, which  
25       are considered to be due to their abrupt vasodilative  
action.

On the other hand, it is disclosed in EP-0425921,  
EP-0459136 and EP-0520423 that benzimidazole  
derivatives have an angiotensin II antagonistic  
30       activities and are useful for the therapy of  
circulatory diseases including hypertension, cardiac  
diseases (cardiac insufficiency, myocardial infarction,  
etc.), cerebral apoplexy, nephritis and  
arteriosclerosis. The mechanism of the action is  
35       considered that the benzimidazole derivatives inhibit  
the binding of angiotensin II having a strong  
vasoconstrictive action to an angiotensin II acceptor.

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And, while, in JPA H3(1991)-27362 and JPA H5(1993)-132467, it is disclosed that an imidazole derivative having angiotensin II antagonistic action is administered together with a diuretic agent or a calcium antagonistic agent.

Object of the invention

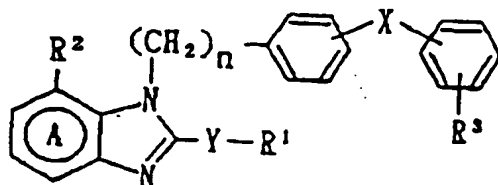
The invention is intended, by combination of a compound having angiotensin II antagonistic action or a salt thereof with a compound having diuretic action or a compound having calcium antagonistic activity, to perform especially remarkable effects, to reduce undesirable side effects and to cover up defects observed in administration of a medicine consisting of a single component.

Summary of the invention

Circumstances being such as above, the present inventors have made extensive and intensive studies on the effects of co-use of a benzimidazole derivative having angiotensin antagonistic activity with a compound having diuretic activity or a compound having calcium antagonistic activity, and, as a result, they have found that the co-use performs especially remarkable effects which were not observed in the administration of the respective compounds singly, thus accomplishing the present invention.

More specifically, the present invention relates to

(1) a pharmaceutical composition for angiotensin II-mediated diseases, which comprises a compound having angiotensin II antagonistic activity of the formula (I):



(I)

wherein  $R^1$  is H or an optionally substituted hydrocarbon residue;  $R^2$  is an optionally esterified carboxyl group;  $R^3$  is a group capable of forming an anion or a group convertible thereinto; X is a covalent bond between the 2 phenyl rings or a spacer having a chain length of 1 to 2 atoms as the linear moiety between the adjoining phenylene group and phenyl group; n is 1 or 2; the ring A is a benzene ring having 1 or 2 optional substituents in addition to  $R^2$ ; and Y is a bond, -O-, -S(O)m- (wherein m is 0, 1 or 2) or -N( $R^4$ )- (wherein  $R^4$  is H or an optionally substituted alkyl group) or a pharmaceutically acceptable salt thereof in combination with a compound having diuretic activity or a compound having calcium antagonistic activity, and (2) a method for the prophylaxis or treatment of angiotensin II-mediated diseases in a mammal which comprises administering an effective amount of a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof in combination with an effective amount of a compound having diuretic activity or a compound having calcium antagonistic activity.

Detailed description of the invention

The compounds to be used for the pharmaceutical composition of this invention are those represented by the above-mentioned formula (I). One of the most remarkable structural characteristic of the compounds results when  $R^2$  is an optionally esterified carboxyl group and  $R^3$  is a group capable of forming anion or a group convertible thereinto. By having such a specific structure as above, the compounds (I) have a very strong angiotensin II antagonistic action.

In formula (I),  $R^1$  stands for H or an optionally substituted hydrocarbon residue.

Examples of the hydrocarbon residue represented by  $R^1$  include alkyl, alkenyl, alkynyl, cycloalkyl, aryl

and aralkyl groups. Among them alkyl, alkenyl and cycloalkyl groups are preferable.

5 The alkyl group represented by  $R^1$  is a straight chain or branched lower alkyl group having 1 to about 8 carbon atoms, as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, i-pentyl, hexyl, heptyl or octyl.

10 The alkenyl group represented by  $R^1$  is a straight chain or branched lower alkenyl group having 2 to about 8 carbon atoms, as exemplified by vinyl, propenyl, 2-butenyl, 3-butenyl, isobutenyl or 2-octenyl.

15 The alkynyl group represented by  $R^1$  is a straight chain or branched lower alkynyl group having 2 to about 8 carbon atoms, as exemplified by ethynyl, 2-propynyl, 2-butylnyl, 2-pentylnyl or 2-octynyl.

The cycloalkyl group represented by  $R^1$  is a lower cycloalkyl group having 3 to about 6 carbon atoms, as exemplified by cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

20 The above mentioned alkyl, alkenyl, alkynyl or cycloalkyl group may optionally be substituted with hydroxyl group, an optionally substituted amino group (e.g. amino, N-lower ( $C_{1-4}$ ) alkylamino or N,N-dilower ( $C_{1-4}$ ) alkylamino), halogen, a lower ( $C_{1-4}$ ) alkoxy group, 25 a lower ( $C_{1-4}$ ) alkylthio group.

The aralkyl group represented by  $R^1$  is, for example, a phenyl-lower ( $C_{1-4}$ ) alkyl such as benzyl or phenethyl, and the aryl group represented by  $R^1$  is, for example, phenyl.

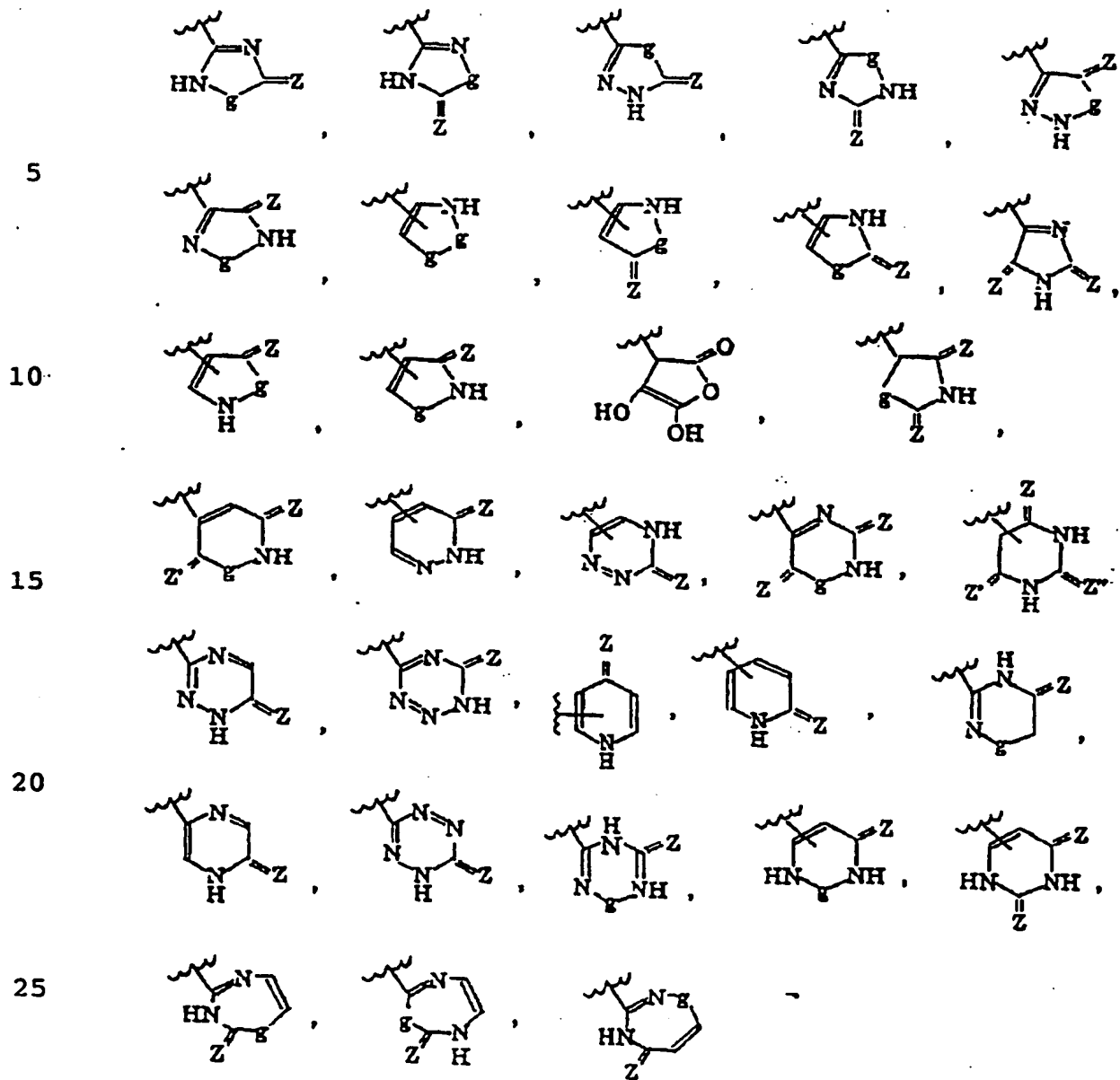
30 The above mentioned aralkyl or aryl group may optionally have, on any position of its benzene ring, for example, halogen (e.g. F, Cl or Br), nitro, an optionally substituted amino group (e.g. amino, N-lower ( $C_{1-4}$ ) alkylamino or N,N-dilower ( $C_{1-4}$ ) alkylamino), 35 lower ( $C_{1-4}$ ) alkoxy (e.g. methoxy or ethoxy), lower ( $C_{1-4}$ )

4) alkylthio (e.g. methylthio or ethylthio) or lower (C<sub>1-4</sub>) alkyl (e.g. methyl or ethyl).

Among the above mentioned groups represented by R<sup>1</sup>, optionally substituted alkyl, alkenyl or cycloalkyl groups (e.g. a lower (C<sub>1-3</sub>) alkyl, lower (C<sub>2-3</sub>) alkenyl or lower (C<sub>3-6</sub>) cycloalkyl group optionally substituted with hydroxyl group, amino group, halogen or a lower (C<sub>1-4</sub>) alkoxy group) are preferable.

Y stands for a bond, -O-, -S(O)<sub>m</sub>- (wherein m is 0, 1 or 2) or -N(R<sup>4</sup>)- (wherein R<sup>4</sup> is hydrogen or an optionally substituted lower alkyl group). Y is preferably a bond, -O-, -S- or -N(R<sup>4</sup>)- (wherein R<sup>4</sup> is hydrogen or a lower (C<sub>1-4</sub>) alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl)).

With respect to formula (I) above, the group for R<sup>3</sup>, capable of forming an anion (a group having a hydrogen atom capable of leaving as a proton), or a group capable of changing thereto, is exemplified by 5- to 7- membered (preferably 5- or 6- membered) monocyclic heterocyclic ring residues which contain one or more of N, S and O and which may be substituted (preferably N-containing heterocyclic residues having a hydrogen atom capable of leaving as a proton), and groups capable of changing thereto in vivo. Such groups include the following:

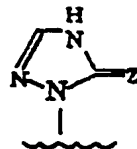
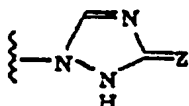
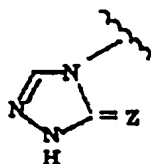


30 The chemical bond between the group for  $R^3$  and the partner phenyl group may be a carbon-carbon bond as shown above, or a nitrogen-carbon bond via one of the several nitrogen atoms when the symbol g stands for -NH- in the above formulas. For instance,

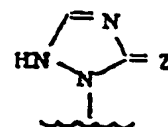
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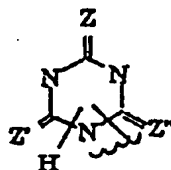
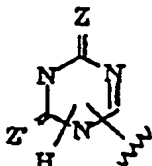
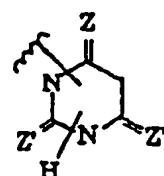
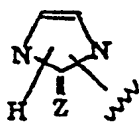
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OF



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etc.

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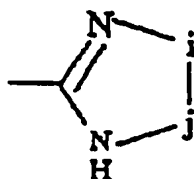
(O)m

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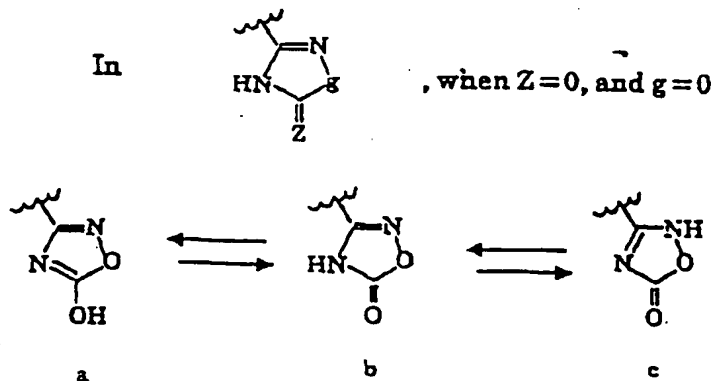
group or sulfinyl group as proton acceptor simultaneously.

And, while the heterocyclic residue represented by  $R^3$  may form a condensed ring by connecting the substituents on the ring, it is preferably a 5- to 6-membered ring, more preferably a 5-membered heterocyclic residue. Especially, groups represented by the formula



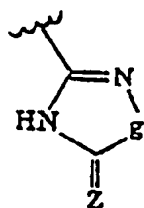
wherein  $i$  stands for  $-O-$  or  $-S-$ ;  $j$  stands for  $>C=O$ ,  $>C=S$  or  $>S(O)m$ ;  $m$  stands for the integer 0, 1 or 2 (in particular, 2,5-dihydro-5-oxo-1,2,4-oxadiazole-3-yl; 2,5-dihydro-5-thioxo-1,2,4-oxadiazole-3-yl; 2,5-dihydro-5-oxo-1,2,4-thiadiazole-3-yl) are preferable.  $R^3$  can be substituted at the ortho, meta or para position of the phenyl group, most preferably at the ortho position.

In addition, the above-mentioned heterocyclic residue ( $R^3$ ) have the following tautomeric isomers:



the three tautomeric isomers a, b and c exist.





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The heterocyclic residue represented by the above formula comprises all of these a, b and c.

Moreover,  $R^3$  may be a carboxyl group, tetrazolyl group, trifluoromethanesulfonamide group ( $-NHSO_2CF_3$ ), phosphate group, sulfonic group, cyano group, or lower ( $C_{1-4}$ ) alkoxy carbonyl group; these groups each may be protected by an optionally substituted lower alkyl or acyl group. Any group capable of forming an anion biologically or physiologically (e.g. through biological reactions such as oxidation, reduction or hydrolysis caused by enzymes in the body) or chemically, or a group capable of changing thereto is acceptable.

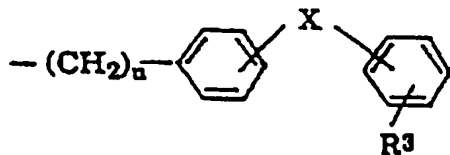
As  $R^3$ , a tetrazolyl or carboxyl (preferably tetrazolyl) group optionally protected by an optionally substituted lower ( $C_{1-4}$ ) alkyl (e.g., methyl, triphenylmethyl, methoxymethyl, ethoxymethyl, p-methoxybenzyl, p-nitrobenzyl, etc.) or acyl (e.g., lower ( $C_{2-5}$ ) alkanoyl, benzoyl, etc.) group is preferable.  $R^3$  can be replaced at the ortho, meta or para position of the phenyl group, most preferably at the ortho position.

X stands for a covalent bond between the 2 phenyl rings or a spacer having a chain length of 1 to 2 atoms as the linear moiety between the adjoining phenylene group and phenyl group. Preferably, X is a covalent bond. The spacer having a chain length of 1 to 2 atoms may consist of a divalent chain in which the number of atoms composing the straight chain portion is either 1 or 2, and may have a side chain. For example, a lower ( $C_{1-4}$ ) alkylene,  $-CO-$ ,  $-O-$ ,  $-S-$ ,  $-NH-$ ,  $-CO-NH-$ ,  $-O-CH_2-$ ,

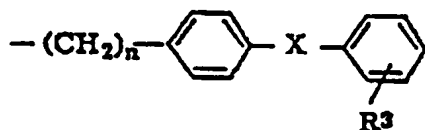
-S-CH<sub>2</sub>-, -CH=CH-, etc. are listed.

n stands for the integer 1 or 2 (preferably 1).

The formula represented by the above-mentioned R<sup>3</sup>, X and n:



is preferably represented by the formula:



R<sup>2</sup> in formula (I) is an optionally esterified carboxyl group.

The optionally esterified carboxyl group as R<sup>2</sup> includes the group represented by the formula -CO-D [wherein D stands for a hydroxyl group or an optionally substituted alkoxyl group (e.g., a lower (C<sub>1-6</sub>) alkoxyl group whose alkyl portion is optionally substituted with a hydroxyl, optionally substituted amino (e.g., amino, dimethylamino, diethylamino, piperidino, morpholino, etc.), halogen, lower (C<sub>1-6</sub>) alkoxyl, lower (C<sub>1-6</sub>) alkylthio or optionally substituted dioxolanyl (e.g., 5-methyl-2-oxo-1,3-dioxolane-4-yl, etc.) group, or the group represented by the formula -O-CH(R<sup>6</sup>)-OCOR<sup>5</sup> [wherein R<sup>6</sup> stands for H, a lower (C<sub>1-6</sub>) straight chain or branched alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl neopentyl, etc.), a lower (C<sub>2-6</sub>) straight chain or branched alkenyl group or a lower (C<sub>3-8</sub>) cycloalkyl group (e.g., cyclopentyl, cyclohexyl, cycloheptyl, etc.); R<sup>5</sup> stands for a lower (C<sub>1-6</sub>) straight chain or branched alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, etc.),

- a lower (C<sub>2-6</sub>) straight chain or branched alkenyl group, a lower (C<sub>3-8</sub>) cycloalkyl group (e.g., cyclopentyl, cyclohexyl, cycloheptyl, etc.), a lower (C<sub>1-3</sub>) alkyl group substituted with C<sub>3-8</sub> cycloalkyl (e.g.
- 5 cyclopentyl, cyclohexyl, cycloheptyl) or an optionally substituted aryl group such as phenyl group (e.g., benzyl, p-chlorobenzyl, phenetyl, cyclopentylmethyl, cyclohexylmethyl, etc.), a lower (C<sub>2-3</sub>) alkenyl group optionally substituted with C<sub>3-8</sub> cycloalkyl or an
- 10 optionally substituted aryl group such as phenyl (e.g., cinnamyl, etc. having alkenyl moiety such as vinyl, propenyl, allyl and isopropenyl, etc.), an aryl group such as optionally substituted phenyl (e.g., phenyl, p-tolyl, naphthyl, etc.), a lower (C<sub>1-6</sub>) straight chain or
- 15 branched alkoxyl group (e.g., methoxyl, ethoxyl, n-propoxyl, isopropoxyl, n-butoxyl, isobutoxyl, sec-butoxyl, t-butoxyl, n-pentyloxyl, isopentyloxyl, neopentyloxyl, etc.), a lower (C<sub>2-8</sub>) straight chain or branched alkenyloxyl group (e.g., allyloxyl,
- 20 isobutenyloxyl, etc.), a lower (C<sub>3-8</sub>) cycloalkyloxyl group (e.g., cyclopentyloxyl, cyclohexyloxyl, cycloheptyloxyl, etc.), a lower (C<sub>1-3</sub>) alkoxyl group substituted with a C<sub>3-8</sub> cycloalkyl (e.g., cyclopentyl, cyclohexyl, cycloheptyl, etc.) or an aryl group such as
- 25 optionally substituted phenyl (e.g., benzyloxy, phenethyloxy, cyclopentylmethyloxy and cyclohexylmethyloxy having alkoxy moiety such as methoxy, ethoxy, n-propoxy and isopropoxy), a lower (C<sub>2-3</sub>) lower alkenyloxy group substituted with a C<sub>3-8</sub>
- 30 cycloalkyl (e.g., cyclopentyl, cyclohexyl, cycloheptyl, etc.) or an optionally substituted aryl group such as phenyl group (e.g., cinnamyloxy etc. having alkenyloxy moiety such as vinyloxy, propenyloxy, allyloxy, isopropenyloxy, etc.), or an optionally substituted
- 35 aryloxyl group such as phenoxyl (e.g., phenoxyl, p-nitrophenoxyl, naphtoxyl, etc.,))}. The substituent

for  $R^2$  may be a group actually or potentially capable of forming an anion [e.g., tetrazolyl group, trifluoromethanesulfonamide group, phosphate group or sulfonic group optionally protected by an alkyl {e.g., lower ( $C_{1-4}$ ) alkyl, etc.} or acyl {e.g., lower ( $C_{2-5}$ ) alkanoyl, optionally substituted benzoyl, etc.} group]. For example, the following substituents are listed: - COOH and its salts, -COOMe, -COOEt, -COOtBu, -COOPr, pivaloyloxymethoxycarbonyl, 1-

(cyclohexyloxycarbonyloxy)ethoxycarbonyl, (5-methyl-2-oxo-1,3-dioxolane-4-yl)methoxycarbonyl, acetoxymethoxycarbonyl, propionyloxymethoxycarbonyl, n-butylloxymethoxycarbonyl, isobutylloxymethoxycarbonyl, 1- (ethoxycarbonyloxy)ethoxycarbonyl, 1- (acetoxy)ethoxycarbonyl, 1- (isobutylloxy)ethoxycarbonyl, cyclohexylcarbonyloxymethoxycarbonyl, benzoyloxymethoxycarbonyl, cinnamiloxy carbonyl and cyclopentylcarbonyloxymethoxycarbonyl, etc..

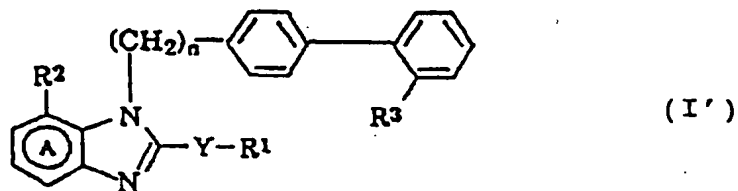
Furthermore,  $R^2$  may be any of the groups actually or potentially capable of forming an anion (e.g.,  $COO^-$  or its derivatives, etc.) under biologic or physiologic conditions (e.g., oxidation or reduction induced by an enzyme present in the living body; *in vivo* reaction such as hydrolysis) or chemically.  $R^2$  may also be a carboxyl group or its prodrug.  $R^2$  may be a group capable of being biologically or chemically biotransformed to an anion.

Among the groups described as  $R^2$ , preferable ones include carboxyl, esterified carboxyl (e.g., methyl ester, ethyl ester or an ester formed by binding of a group represented by the above mentioned formula  $-O-CH(R^6)-OCOR^5$  to carbonyl) and optionally protected tetrazolyl, carboaldehyde and hydroxymethyl.

In general formula (I), ring A may have, in

addition to the group represented by  $R^2$ , another substituent, e.g., a halogen atom (e.g., F, Cl, Br, etc.), cyano group, nitro group, lower ( $C_{1-4}$ ) alkyl group, lower ( $C_{1-4}$ ) alkoxy group, optionally substituted amino group (e.g., amino, N-lower ( $C_{1-4}$ ) alkylamino (e.g., methylamino, etc.), N,N-dilower ( $C_{1-4}$ ) alkylamino (e.g., dimethylamino, etc.), N-arylamino (e.g., phenylamino, etc.), alicyclic amino (e.g., morpholino, piperidino, piperazino, N-phenylpiperazino, etc.), etc.), a group represented by the formula  $-CO-D'$  [wherein  $D'$  stands for a hydroxyl group or a lower ( $C_{1-4}$ ) alkoxy group whose alkyl moiety may be substituted with a hydroxyl group, lower ( $C_{1-4}$ ) alkoxy group, lower ( $C_{2-6}$ ) alkanoyloxy (e.g., acetoxy, pivaloyloxy, etc.) or lower ( $C_{1-6}$ ) alkoxycarbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, cyclohexyloxy, etc.) group], or tetrazolyl, trifluoromethanesulfonamide, phosphoric acid or sulfonic acid group which may be protected by lower ( $C_{1-4}$ ) alkyl or acyl group (e.g., lower ( $C_{2-3}$ ) alkanoyl, optionally substituted benzoyl, etc.); among them, a lower ( $C_{1-4}$ ) alkyl group and a halogen group are preferable. Of these substituents, one or two may simultaneously substitute for groups at available positions in the ring.

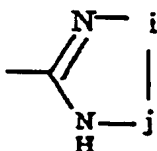
Among the compounds represented by the above mentioned formula (I), compounds represented by formula (I') are preferred:



[wherein ring A stands for a benzene ring which may have another 1 or 2 substituents in addition to the

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group represented by  $R^2$ ;  $R^1$  stands for H or an optionally substituted lower ( $C_{1-6}$ ) alkyl (preferably lower ( $C_{1-4}$ ) alkyl); Y stands for O, N(H) or S;  $R^2$  is a group represented by the formula  $-CO-D''$  [wherein  $D''$  stands for hydroxyl group, or a lower ( $C_{1-4}$ ) alkoxy whose alkyl moiety is optionally substituted with hydroxyl group, amino, halogen, a lower ( $C_{2-6}$ ) alkanoyloxy (e.g. acetyloxy and pivaloyloxy, etc.), lower ( $C_{4-7}$ ) cycloalkanoyloxy, lower ( $C_{1-6}$ ) alkoxy;  $R^3$  stands for a tetrazolyl, carboxyl group or groups represented by the formula,



wherein  $i$  stands for  $-O-$  or  $-S-$ ;  $j$  stands for  $>C=O$ ,  $>C=S$  or  $>S(O)_m$ ; and  $m$  stands for the integer 0, 1 or 2, which are optionally protected with optionally substituted lower ( $C_{1-4}$ ) alkyl (e.g. methyl, triphenylmethyl, methoxymethyl, acetyloxymethyl, methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, 1-(cyclohexyloxycarbonyloxy)ethyl and pivaloyloxymethyl, etc.) or an acyl group (e.g. a lower  $C_{2-5}$  alkanoyl and benzoyl, etc.);  $n$  is 1 or 2.

In the formula (I'), substituents on the optionally substituted lower alkyl for  $R^1$  include a hydroxyl group, an amino group, halogen and a lower ( $C_{1-4}$ ) alkoxy group.

In the formula (I'), ring A is a benzene ring which may have a substituent, in addition to the group  $R^2$ , such as a halogen (e.g., F, Cl, Br), lower ( $C_{1-4}$ ) alkyl, lower ( $C_{1-4}$ ) alkoxy, nitro, a group represented

by the formula  $-CO-D'$ , wherein  $D'$  represents a hydroxyl group or a lower ( $C_{1-4}$ ) alkoxy whose alkyl moiety may be substituted with a hydroxyl group, lower ( $C_{1-4}$ ) alkoxy, lower ( $C_{2-6}$ ) alkanoyloxy (e.g., acetoxy, pivaloyloxy, etc.) or lower ( $C_{1-6}$ ) alkoxycarbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, cyclohexyloxycarbonyloxy), or an amino which may be substituted with a lower ( $C_{1-4}$ ) alkyl (preferably a substituent such as a lower ( $C_{1-4}$ ) alkyl or halogen). More preferably, A is a benzene ring which has no substituent in addition to the group represented by the formula  $R^2$ .

As the salt thereof, pharmaceutically acceptable salts are used, e.g., a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. Inorganic bases appropriate to form the salt include alkali metals such as sodium or potassium, alkali earth metals such as calcium and magnesium or aluminum, and ammonia. Organic bases appropriate to form the salt include trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, and N,N'-dibenzylethylenediamine. Inorganic acids appropriate to form the salt include hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. Organic acids appropriate to form the salt include formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. Basic amino acids to form the salt include arginine, lysine and ornithine. Acidic amino acids to form the salt include aspartic acid and glutamic acid.

As an active ingredient of the present invention, the compounds having angiotensin II antagonistic

activity described in the Examples of Japan Provisional Publication No. 364171/1992 and EP520423 are preferred. The compounds represented by general formula (I) were, for instance, disclosed in Provisional Publication Nos. 9373/1992 and 364171/1992, and EP520423, and can be manufactured as described in these publications.

As compounds having diuretic activity, while mention is made of amiloride, chlorothiazide, hydrochloride, benzthiazide, ticrynafen, acetazolamide, aminophylline, cyclothiazide, trichloromethiazide, cyclopenthiazide, hydrochlorothiazide, methyclothiazide, benzylhydrochlorothiazide, penfluthiazide, ethiazide, hydroflumethiazide, polythiazide, clofenamide, chlorthalidone, cyclothiazide, bendroflumethiazide, meticrane, tripamide, methrazone, indapamide, quinethazone, furosemide, bumetanide, mefruside, azosemide, ethacrynic acid, sodium ethacrylate, piretanide, spironolactone, potassium canrenoate and triamterene, mention is also made of a mixture of them or a combination of them.

As compounds having calcium antagonistic activity, while mention is made of diltiazem hydrochloride, terodiline hydrochloride, nicardipine hydrochloride, valnidipine hydrochloride, flunarizine hydrochloride, varapamyl hydrochloride, manidipine hydrochloride, cinnarizine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, nildipine, nimodipine, penidipine and benidipine; mention is also made of a mixture of them or a combination of them.

The angiotensin II mediated diseases include hypertension, cardiac insufficiency, ischemic peripheral circulation disturbances, myocardial ischemia, vein insufficiency, progressive cardiac insufficiency after myocardial infarction, diabetic nephritides, nephritis, arteriosclerosis,



hyperaldosteronism, dermatosclerosis,  
glomerulosclerosis, renal insufficiency, diseases of  
central nervous system, sensory disturbances including  
Alzheimer's disease, deficiency of memory, depression,  
5 amnesia and senile dementia, anxiety neurosis,  
catatonia or indisposition, glaucoma, intraocular high  
tension.

10 The pharmaceutical composition of angiotensin II-  
mediated diseases, whose effective components being a  
compound having angiotensin II antagonistic activity  
represented by the formula (I) compound or a salt  
thereof and a compound having diuretic activity or a  
15 compound having calcium antagonistic activity, can be  
administered orally or non-orally in the form of, for  
example, granules, powders, tablets, capsules, syrup,  
suppositories, injections, emulsions, elixir,  
suspensions or solutions, by mixing these effective  
components, individually or simultaneously, with  
20 pharmaceutically acceptable carriers, excipients,  
binders, diluents or the like. In the case of  
formulating the effective components individually,  
while thus individually formulated agents can be  
administered in the form of their mixture prepared by  
using, for example, a diluent when administered, the  
25 individually formulated agents can also be administered  
separately or simultaneously or with time intervals to  
the one and same subject.

30 The pharmaceutical composition for angiotensin II-  
mediated diseases of the present invention can be  
formulated in accordance with conventional procedures.  
In the present specification, "non-orally" include  
subcutaneous injection, intravenous injection,  
intramuscular injections, intraperitoneal injection or  
instillation. Injectable preparations, for example,  
35 sterile injectable aqueous suspensions or oil  
suspensions can be prepared by known procedure in the

fields concerned, using a suitable dispersant or wetting agent and suspending agent. The sterile injections may be in the state of, for example, a solution or a suspension, which is prepared with a non-toxic diluent administrable non-orally, e.g. an aqueous solution, or with a solvent employable for sterile injection. Examples of usable vehicles or acceptable solvents include water, Ringer's solution and an isotonic aqueous saline solution. Further, a sterile non-volatile oil can usually be employed as solvent or suspending agent.

Any non-volatile oil and a fatty acid can be used for this purpose, which includes natural or synthetic or semi-synthetic fatty acid oil or fatty acid, and natural or synthetic or semi-synthetic mono- or di- or tri-glycerides.

Rectal suppositories can be prepared by mixing the drug with a suitable non-irritable vehicle, for example, cocoa butter and polyethylene glycol, which is in the solid state at ordinary temperatures, in the liquid state at temperatures in intestinal tubes and melts in rectum to release the drug.

As a solid formulation for oral administration, mention is made of powders, granules, tablets, pills and capsules as referred to in the above. In such formulations as exemplified above, the active component compounds can be mixed with at least one additive, for example, sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. These formulations can contain, as in conventional cases, further additives, for example, an inactive diluent, a lubricant such as magnesium stearate, a preservative such as paraben or sorbic acid, an anti-oxidant such as

ascorbic acid,  $\alpha$ -tocopherol or cysteine, a  
disintegrator, a binder, a thickening agent, a buffer,  
a sweetener, a flavoring agent and a perfuming agent.  
Tablets and pills can further be prepared with enteric  
5 coating. Examples of liquid preparations for oral  
administration include pharmaceutically acceptable  
emulsions, syrups, elixirs, suspensions and solutions,  
which may contain an inactive diluent, for example,  
water, which is conventionally employed in the field  
10 concerned.

The pharmaceutical composition of this invention  
against angiotensin II-mediated diseases are less  
toxic, which is used as a medicine for animals,  
especially mammals (e.g. human being, dog, rabbit,  
15 mouse, etc.), can be advantageously used for  
angiotensin II-mediated diseases.

The pharmaceutical composition of this invention  
for angiotensin II-mediated diseases formulated by  
combining a compound having angiotensin II antagonistic  
20 activity or a salt thereof with a compound having  
diuretic activity or a compound having calcium  
antagonistic activity. This composition serves to  
decrease the dosages of the individual effective  
components, and, as a result, suppresses undesirable  
25 side effects observed in the case of administering the  
respective compounds singly.

007533-01204

Also, by incorporation of polymers of alkylene oxide into a formulation comprising a compound having angiotensin II antagonistic activity represented by the formula (I), or a salt thereof and a compound having diuretic activity or a compound having calcium antagonistic activity, decomposition of the active components is remarkably suppressed to afford a stable composition.

The above polymers of alkylene oxide may be evenly admixed with the active components in preparation of pharmaceutical compositions for oral use so that more stable compositions are produced. Furthermore, among the polymers of alkylene oxide, any one may be soluble or insoluble in water.

As the polymer of alkylene oxide, use is made of those having a molecular weight of 1,000 to 10,000 (e.g. polyethylene glycol 6000). Examples of the alkylene oxide include ethylene oxide, propylene oxide, trimethylene oxide and tetrahydrofuran (preferably ethylene oxide).

The polymers of alkylene oxide may be used singly or as a mixture of two or more of them.

The polymers are added to the active components in a solid or liquid state.

The method for preparing a pharmaceutical composition using polymers of alkylene oxide is more conveniently applied to a solid composition (e.g., granules and tablets, preferably tablets) prepared by molding (e.g. granulation or molding under elevated pressure).

Preparation of a solid composition is usually conducted by incorporating polymers of alkylene oxide into the active components, followed by subjecting the mixture to molding. The incorporation is conducted by a method conventionally employed in the field of pharmaceutical preparations, for example, mixing, massing, kneading, sieving and stirring. For example, polymers of alkylene oxide are directly added to the active components and to make a mixture (addition in powdery state), or a solvent is added to the mixture, followed by conventional granulating and drying. Alternatively, polymers of alkylene oxide are dissolved in a suitable solvent, then the solution is mixed with the active

components, followed by conventional kneading, granulating and drying (addition in liquid state). Further, a liquid material containing polymers of alkylene oxide and a liquid material containing the active components can be independently sprayed onto a powdery material such as an excipient, followed by mixing the resultant material. In the case of "addition in liquid state", any solvent which does not exert undesirable influence on the active component, for example, water, dimethylformamide, acetone, ethanol, propyl alcohol, isopropyl alcohol, butyl alcohol, methylene chloride and trichloroethane, can be employed. After completing the blending, the material is subjected to a conventional molding process under elevated pressure to prepare tablets containing the active components. The molding under elevated pressure means that a material is compressed under elevated pressure into a desired form, and it refers to, most generally, tabletting. Incorporation of polymers of alkylene oxide as described above serves to minimize crystalline disorder possibly caused in the steps of kneading, granulating and molding under elevated pressure and is considered to further serve advantageously to improve the moldability and to lower the pressure to be elevated. In the method of preparing the composition, a variety of additives to be employed for solid compositions can be added in an adequate step. These additives are exemplified by excipients such as crystalline cellulose (e.g. Avicel PH 101 (manufactured by Asahi Chemical Industry Co., Ltd.), carboxymethyl cellulose calcium, corn starch, wheat starch, lactose, sucrose, glucose, calcium sulfate, calcium phosphate or sodium chloride, binders such as gum arabic, gelatin, methyl cellulose, polyvinyl pyrrolidone, hydroxypropyl cellulose (hereinafter sometimes abbreviated as HPC) or hydroxypropylmethyl cellulose, lubricants such as magnesium stearate, talc, synthetic aluminum silicate, sodium lauryl sulfate, boric acid, magnesium oxide or paraffin, colorants, flavoring agents, odor-improving agents, etc. Furthermore, the composition may be prepared into coated tablets as well.

0075336-011201

The coating process may be accomplished by a known method. Use is made of conventional coating agents (e.g., hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose and polyvinyl pyrrolidone). Polyethylene glycol 6000, polysorbate, titanium oxide and pigments such as red iron oxide are used as auxiliary agents for coatings.

In the stabilized pharmaceutical composition for oral use prepared by admixing polymers of alkylene oxide with the active components, the amount of the polymers is 0.005 to 0.15 weight, preferably 0.01 to 0.1 weight, preferably 0.02 to 0.05 weight per 1 weight of the composition.

30 The dose of a specific patient is dependent on the age, body weight, general health conditions, sex, diet, dose interval, administration routes, excretion rate, combinations of drugs and conditions of the diseases treated, while taking these and other necessary factors into consideration.

35 Typical daily doses of the compositions having various combinations of a compound represented by the formula (I) or a salt thereof and a compound having diuretic activity or a compound having calcium

antagonistic activity are within the range of from about 1/50 of the minimal recommendable clinical dose to maximal recommendable dose in the case of practical administration of these compounds individually.

5           For example, a compound represented by the formula (I) having an angiotensin II antagonistic activity to be administered at a dose of about 0.01 to 150 mg/patient/day can be administered at a dose of about 0.0002 to 150 mg/patient/day, preferably 0.001 to 60  
10 mg/patient/day, more preferably 0.01 to 20 mg/patient/day by combining with the following daily doses of the following compounds:  
trichloromethiazide (1 to 8 mg), cyclopenthiazide (0.25 to 1 mg), cyclothiazide (1 to 2 mg), chlorothiazide  
15 (500 to 1000 mg), bendroflumethiazide (2 to 10 mg), hydrochlorothiazide (5 to 200 mg), methyclothiazide (2.5 to 5 mg), benzylhydrochlorothiazide (4 to 16 mg), penfluthiazide (1.5 to 7.5 mg), ethiazide (2.5 to 10 mg), hydroflumethiazide (10 to 200 mg), polythiazide  
20 (0.25 to 4 mg), meticrane (150 to 300 mg), chlorothalidone (50 to 200 mg), tripamide (15 to 30 mg), methrazone (2.5 to 5 mg), indapamide (0.5 to 2 mg), quinethazone (25 to 150 mg), clofenamide (50 to 400 mg), furosemide (20 to 500 mg), bumetanide (0.5 to  
25 2 mg), mefruside (1.25 to 50 mg), diltiazem hydrochloride (10 to 200 mg), nicardipine hydrochloride (3 to 40 mg), valnidipine hydrochloride (2 to 15 mg), flunarizine hydrochloride (2 to 10 mg), verapamil hydrochloride (2 to 80 mg), manidipine hydrochloride (2  
30 to 20 mg), cinnarizine (10 to 50 mg), nisoldipine (2 to 10 mg), nitrendipine (2 to 10 mg), nifedipine (3 to 40 mg), nilvadipine (1 to 8 mg), or benidipine (2 to 8 mg). Needless to say, while these dosage ranges can be adjusted by a necessary unit base for dividing a daily  
35 dose, as described above, such doses are decided depending on the diseases to be treated, conditions of

such diseases, the age, body weight, general health conditions, sex, diet of the patient then treated, dose intervals, administration routes, excretion rate, and combinations of drugs, while taking these and other  
5 necessary factors into consideration.

The desired unit dose of the composition of this invention is administered once or twice daily (preferably once).

For example, the unit dose composition contains  
10 about 0.0002 to 150 mg, preferably 0.001 to 60 mg, more preferably 0.01 to 20 mg of a compound represented by the formula (I)~ by combining with the following amount of the following compound:

15 trichloromethiazide (1 to 8 mg), cyclopenthiazide (0.25 to 1 mg), cyclothiazide (1 to 2 mg), chlorothiazide (500 to 1000 mg), bendroflumethiazide (2 to 10 mg), hydrochlorothiazide (5 to 200 mg), methyclothiazide (2.5 to 5 mg), benzylhydrochlorothiazide (4 to 16 mg), penfluthiazide (1.5 to 7.5 mg), ethiazide (2.5 to 10  
20 mg), hydroflumethiazide (10 to 200 mg), polythiazide (0.25 to 4 mg), meticrane (150 to 300 mg), chlorothalidone (50 to 200 mg), tripamide (15 to 30 mg), methrazone (2.5 to 5 mg), indapamide (0.5 to 2 mg), quinethazone (25 to 150 mg), clofenamide (50 to  
25 400 mg), furosemide (20 to 500 mg), bumetanide (0.5 to 2 mg), mefruside (1.25 to 50 mg), diltiazem hydrochloride (10 to 200 mg), nicardipine hydrochloride (3 to 40 mg), valnidipine hydrochloride (2 to 15 mg), flunarizine hydrochloride (2 to 10 mg), verapamil  
30 hydrochloride (2 to 80 mg), manidipine hydrochloride (2 to 20 mg), cinnarizine (10 to 50 mg), nisoldipine (2 to 10 mg), nitrendipine (2 to 10 mg), nifedipine (3 to 40 mg), nilvadipine (1 to 8 mg), or benidipine (2 to 8 mg).

35 The composition of this invention as described above is advantageously carried out in combination with



hydrochlorothiazide. The amount of hydrochlorothiazide present in a dosage unit is from about 5 mg to 200 mg, preferably 5 mg to 100 mg, more preferably 5 to 50 mg.

By the following test examples and working examples, the present invention will be illustrated in more detail, and they should not be construed as limiting the invention thereto.

The physiological activities of the composition comprising a compound having angiotensin II antagonistic activity or a salt thereof and a compound having diuretic activity or a compound having calcium antagonistic activity are described by the following test examples.

Test Example 1

Antihypertensive activity in spontaneously hypertensive rats (SHR) by the co-administration with a diuretic drug

Compound 1: ( $\pm$ )-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate

HCT: hydrochlorothiazide

Method: Male SHR of 20 week old were divided into 6 groups (five animals in one group). The respective groups were administered orally with the compound 1 (0.1 or 1 mg/kg, p.o.) or HCT (10 mg/kg, p.o.) alone or both drugs simultaneously once a day for two weeks. On the first, 7th and 14th day at 5 hr after the administration, blood pressure of each test animal was measured by the tail cuff method under unanesthesia.

Results: As shown in Table 1. Single dose of HCT (10mg/kg/day, p.o.) did not show antihypertensive action. The compound 1 (0.1 and 1 mg/kg/day) showed dose dependent antihypertensive action. Efficiency of the antihypertensive activity of the compound 1 was enhanced by its co-administration with HCT. The

antihypertensive activity observed by the combination of the compound 1 (0.1 mg/kg) and HCT was stronger or substantially the same as that observed by administering the compound 1 alone (1 mg/kg). This result shows that the combination of both drugs can decrease the dosages of the respective drugs.

Table 1

Antihypertensive activity by the combination of compound 1 and the diuretic drug in spontaneously hypertensive rats

Test group (dosage) mg/kg/day, p.o.	Before admin.	1 day (blood pressure : mmHg)	1 week	2 weeks
Control -	183 ± 2	183 ± 1	179 ± 2	181 ± 4
HCT (10)	186 ± 3	178 ± 3	177 ± 3	181 ± 2
Cpd. 1 (0.1)	183 ± 2	161 ± 5	155 ± 3	162 ± 3
Cpd. 1 (1)	186 ± 2	153 ± 5	138 ± 2	135 ± 3
HCT(10)+Cpd.1 (0.1)	186 ± 4	137 ± 5	129 ± 5	139 ± 3
HCT(10)+Cpd.1 (1)	187 ± 2	132 ± 3	106 ± 5	108 ± 4

Numerical values: average values ± standard error

### Test Example 2

Antihypertensive activity in spontaneously hypertensive rats (SHR) by the co-administration with a calcium antagonistic drug

Compound 1: (±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate

MDP: manidipine

Method: Male SHR of 20 week old were divided into six groups (five animals per group). The respective groups were administered orally with the compound 1 (0.1 or 1 mg/kg, p.o.) or MDP (3 mg/kg, p.o.) alone or with a mixture of them once a day for two weeks. On the first, 7th and 14th day at 5 hr after the administration, blood pressure of each test animal was

measured by the tail cuff method under unanesthesia. Results: As shown in Table 2. Single administration of MDP (3 mg/kg/day, p.o.) showed apparent antihypertensive effect, and the compound 1 (0.1 and 1 mg/kg/day) performed dose dependent antihypertensive effect. The antihypertensive activity of the compound 1 was enhanced by the co-administration with MDP (3 mg/kg/day). The hypotensive activity observed by the co-administration of the compound 1 (0.1 mg/kg) with MDP was stronger or substantially the same as that observed by administering the compound 1 alone (1 mg/kg). This result shows that simultaneous usage of both drugs can decrease in the dosages of the respective drugs.

Table 2

Antihypertensive activity by the combination of compound 1 and the calcium antagonistic drug in spontaneously hypertensive rats

Test group (dosage) mg/kg/day, p.o.	Before admin.	1 day (blood pressure : mmHg)	1 week	2 weeks
Control -	188 ± 3	184 ± 2	181 ± 3	179 ± 1
MDP (3)	190 ± 5	157 ± 2	132 ± 5	136 ± 7
Cpd. 1 (0.1)	190 ± 2	157 ± 2	158 ± 4	160 ± 4
Cpd. 1 (1)	196 ± 3	148 ± 3	131 ± 13	142 ± 4
MDP(3)+Cpd.1 (0.1)	193 ± 4	130 ± 6	128 ± 6	141 ± 5
MDP(3)+Cpd.1 (1)	192 ± 3	127 ± 4	114 ± 4	111 ± 3

Numerical values: average values ± standard error

### Test Example 3

Antihypertensive activity in spontaneously hypertensive rats (SHR) by the co-administration with a diuretic drug

Compound 2: 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazole-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid

HCT: hydrochlorothiazide

Method: Male SHR of 20 week old were divided into 6 groups (five animals in one group). The respective groups were administered orally with the compound 2 (0.1 or 1 mg/kg, p.o.) or HCT (10 mg/kg, p.o.) alone or both drugs simultaneously once a day for two weeks. On the first, 7th and 14th day at 5hr after the administration, blood pressure of each test animal was measured by the tail cuff method under unanesthesia.

Results: As shown in Table 3. Single dose of HCT (10 mg/kg/day, p.o.) did not show antihypertensive action. The compound 2 (0.1 and 1 mg/kg/day) showed dose dependent antihypertensive action. Efficiency of the antihypertensive activity of the compound 2 was enhanced by its co-administration with HCT. The antihypertensive activity observed by the combination of the compound 2 (0.1 mg/kg) and HCT was stronger or substantially the same as that observed by administering the compound 2 alone (1 mg/kg). This result shows that the co-use of both drugs can decrease the dosages of the respective drugs.

Table 3

Antihypertensive activity by the combination of compound 1 and the diuretic drug in spontaneously hypertensive rats

Test group (dosage) mg/kg/day, p.o.	Before admin.	1 day (blood pressure : mmHg)	1 week	2 weeks
Control -	205 ± 5	200 ± 5	202 ± 6	206 ± 5
HCT (10)	206 ± 5	188 ± 5	190 ± 5	195 ± 3
Cpd. 2 (0.1)	215 ± 5	187 ± 6	182 ± 6	191 ± 8
Cpd. 2 (1)	219 ± 7	175 ± 5	161 ± 4	165 ± 3
HCT(10)+Cpd.2 (0.1)	222 ± 11	173 ± 5	168 ± 5	168 ± 3
HCT(10)+Cpd.2 (1)	221 ± 6	170 ± 4	134 ± 3	142 ± 5

Numerical values: average values ± standard error(n=7)

As is apparent from these test examples, the composition comprising the compound having angiotensin II antagonistic activity or a salt thereof and the compound having diuretic activity or the compound having calcium antagonistic activity enhances the action of the respective drug administered singly and can decrease the dosages of the respective drugs. As a result, suppression of the occurrence of undesirable side effects observed when these drugs are administered singly can be expected to a considerable extent.

#### Working Example

#### Formulation Examples

The pharmaceutical composition of angiotensin II-mediated diseases, formulated by combination of a compound having angiotensin II antagonistic activity represented by the formula (I) or a salt thereof and a compound having diuretic activity or a compound having calcium antagonistic activity, can be prepared by the prescriptions described as follows.

##### 1. Capsules

- |     |  |        |
|-----|--|--------|
| (1) | 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid | 1 mg   |
| (2) | hydrochlorothiazide  | 25 mg  |
| (3) | lactose  | 64 mg  |
| (4) | microcrystalline cellulose   | 70 mg  |
| (5) | magnesium stearate   | 10 mg  |
|     | one capsule  | 180 mg |

(1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the remainder of (5), and the whole was filled into a gelatin capsule.

##### 2. Tablets

- |     |  |      |
|-----|--|------|
| (1) | 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid | 1 mg |
|-----|--|------|

5

one tablet 130 mg

10

### 3. Injections

15

one ampoule 130 mg

25

#### 4. Capsules

30

one capsule 180 mg

35

remainder of (5), and the whole formulation was filled into a gelatin capsule.

# 5. Tablets

5	(1) (±)-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylate	1 mg
	(2) hydrochlorothiazide	25 mg
	(3) lactose	71.4 mg
	(4) corn starch	20 mg
10	(5) polyethylene glycol	2.6 mg
	(6) hydroxypropyl cellulose	4 mg
	(7) carmellose calcium	5.6 mg
	(8) magnesium stearate	0.4 mg

one tablet 130 mg

15 (1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

# 20 6. Injections

	(1) disodium 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate	1 mg
	(2) furosemide	20 mg
25	(3) inositol	89 mg
	(4) benzyl alcohol	20 mg

one ampoule 130 mg

(1), (2), (3) and (4) were dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process was conducted under sterile conditions.

# 30 7. Capsules

	(1) 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid	1 mg
35	(2) hydrochlorothiazide	25 mg
	(3) lactose	64 mg

(4) microcrystalline cellulose 70 mg  
(5) magnesium stearate 10 mg  
one capsule 180 mg

5 (1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the remainder of (5), and the whole was filled into a gelatin capsule.

8. Tablets

10 (1) 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid 1 mg  
(2) hydrochlorothiazide 25 mg  
(3) lactose 71.4 mg  
(4) corn starch 20 mg  
15 (5) polyethylene glycol 2.6 mg  
(6) hydroxypropyl cellulose 4 mg  
(7) carmellose calcium 5.6 mg  
(8) magnesium stearate 0.4 mg

one tablet 130 mg

20 (1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

25 9. Capsules

(1) pivaloyloxymethyl 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazol-7-carboxylate 1 mg  
30 (2) hydrochlorothiazide 25 mg  
(3) lactose 64 mg  
(4) microcrystalline cellulose 70 mg  
(5) magnesium stearate 10 mg

one capsule 180 mg

35 (1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the



remainder of (5), and the whole formulation was filled into a gelatin capsule.

10. Capsules

5	(1) ( $\pm$ )-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1- [[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H- benzimidazole-7-carboxylate	2 mg
	(2) manidipine hydrochloride	2 mg
	(3) lactose	96 mg
	(4) microcrystalline cellulose	70 mg
10	(5) magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the remainder of (5), and the whole was filled into a gelatine capsule.

11. Tablets

	(1) ( $\pm$ )-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1- [[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H- benzimidazole-7-carboxylate	2 mg
20	(2) manidipine hydrochloride	2 mg
	(3) lactose	93.4 mg
	(4) corn starch	20 mg
	(5) polyethylene glycol	2.6 mg
	(6) hydroxypropyl cellulose	4 mg
25	(7) carmellose calcium	5.6 mg
	(8) magnesium stearate	0.4 mg
	one tablet	130 mg

(1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

12. Tablets

35	(1) 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4- oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H- benzimidazole-7-carboxylic acid	1 mg
----	--	------

	(2) hydrochlorothiazide	25 mg
	(3) lactose	71.4 mg
	(4) corn starch	20 mg
	(5) polyethylene glycol	2.6 mg
5	(6) hydroxypropyl cellulose	4 mg
	(7) carmellose calcium	5.6 mg
	(8) magnesium stearate	0.4 mg

one tablet 130 mg

(1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the the mixture to compression molding.

### 13. Tablets

15	(1) 2-ethoxy-1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid	2 mg
	(2) manidipine hydrochloride	2 mg
	(3) lactose	93.4 mg
20	(4) corn starch	20 mg
	(5) polyethylene glycol	2.6 mg
	(6) hydroxypropyl cellulose	4 mg
	(7) carmellose calcium	5.6 mg
	(8) magnesium stearate	0.4 mg

25 one tablet 130 mg

(1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granulates were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

### 14. Capsules

	(1) 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid	4 ~ 12 mg
35	(2) hydrochlorothiazide	6.25 mg
	(3) lactose	64 mg

- (4) microcrystalline cellulose 70 mg  
(5) magnesium stearate 10 mg

one capsule 154.25 ~ 162.25 mg

5 (1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the remainder of (5), and the whole was filled into a gelatin capsule.

15. Tablets

- 10 (1) 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid  
4 ~ 12 mg  
(2) hydrochlorothiazide 6.25 mg  
(3) lactose 71.5 mg  
(4) corn starch 20 mg  
15 (5) polyethylene glycol 2.6 mg  
(6) hydroxypropyl cellulose 4 mg  
(7) carmellose calcium 5.6 mg  
(8) magnesium stearate 0.4 mg

one tablet 114.35 ~ 122.35 mg

20 (1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

25 16. Capsules

- (1) (±)-1-(cyclohexyloxycarbonyloxy)ethyl  
2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate  
4 ~ 12 mg  
30 (2) hydrochlorothiazide 6.25 mg  
(3) lactose 64 mg  
(4) microcrystalline cellulose 70 mg  
(5) magnesium stearate 10 mg

one capsule 154.25 ~ 162.25 mg

35 (1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the

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remainder of (5), and the whole was filled into a gelatin capsule.

17. Tablets

- 5 (1)  $(\pm)$ -1-(cyclohexyloxycarbonyloxy)ethyl  
2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]  
methyl]-1H-benzimidazole-7-carboxylate 4 ~ 12 mg  
6.25 mg  
(2) hydrochlorothiazide  
(3) lactose 71.4 mg  
(4) corn starch 20 mg  
10 (5) polyethylene glycol 2.6 mg  
(6) hydroxypropyl cellulose 4 mg  
(7) carmellose calcium 5.6 mg  
(8) magnesium stearate 0.4 mg

one tablet 114.35 ~ 122.35 mg

- 15 (1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7)  
and 1/2 of (8) were mixed and then granulated. To the  
granules were added the remainders of (6), (7) and (8),  
followed by subjecting the mixture to compression  
molding.

20 18. Capsules

- (1) 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]  
methyl]-1H-benzimidazole-7-carboxylic acid  
2 mg  
(2) hydrochlorothiazide 6.25 ~ 25 mg  
25 (3) lactose 64 mg  
(4) microcrystalline cellulose 70 mg  
(5) magnesium stearate 10 mg

one capsule 152.25 ~ 171 mg

- 30 (1), (2), (3), (4) and 1/2 of (5) were mixed and  
then granulated. To the granules was added the  
remainder of (5), and the whole was filled into a  
gelatin capsule.

19. Tablets

- 35 (1) 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]  
methyl]-1H-benzimidazole-7-carboxylic acid  
2 mg

	(2) hydrochlorothiazide	6.25 ~ 25 mg
	(3) lactose	71.5 mg
	(4) corn starch	20 mg
	(5) polyethylene glycol	2.6 mg
5	(6) hydroxypropyl cellulose	4 mg
	(7) carmellose calcium	5.6 mg
	(8) magnesium stearate	0.4 mg

one tablet 112.35 ~ 131.1 mg

(1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

#### 20. Capsules

15	(1) ( $\pm$ )-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylate	2 mg
	(2) hydrochlorothiazide	6.25 ~ 25 mg
20	(3) lactose	64 mg
	(4) microcrystalline cellulose	70 mg
	(5) magnesium stearate	10 mg

one capsule 152.25 ~ 171 mg

(1), (2), (3), (4) and 1/2 of (5) were mixed and then granulated. To the granules was added the remainder of (5), and the whole was filled into a gelatin capsule.

#### 21. Tablets

30	(1) ( $\pm$ )-1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylate	2 mg
	(2) hydrochlorothiazide	6.25 ~ 25 mg
	(3) lactose	71.4 mg
	(4) corn starch	20 mg
35	(5) polyethylene glycol	2.6 mg
	(6) hydroxypropyl cellulose	4 mg

(7) carmellose calcium	5.6 mg
(8) magnesium stearate	0.4 mg

one tablet      112.35 ~ 131.1 mg

(1), (2), (3), (4), (5), 2/3 of (6), 2/3 of (7) and 1/2 of (8) were mixed and then granulated. To the granules were added the remainders of (6), (7) and (8), followed by subjecting the mixture to compression molding.

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	